

COMPOUND AND DERIVATIVE OF GABAPENTIN

BACKGROUND OF THE INVENTION

5 1. Field of the Invention

The present invention relates to a compound or derivatives of gabapentin, especially a compound or derivatives of gabapentin for medical purposes.

10 2. Description of Related Art

Gabapentin is used widely in the treatment of epilepsy and in pain syndrome therapy and in 2001; its global sales reached US\$1.47 billion. However, the drug has poor oral bioavailability, and 900 to 4800 mg in dosage for three times per day is required to approach the desired efficacy.

15 However, it was found that the greater dosage in administration did not result in relative adsorption enhancement. Moreover, the change of the administration method did not increase the oral bioavailability. Therefore, according to the prodrug concepts, if the gabapentin can be designed as a highly bioavailable prodrug to reduce the dosage amount and regime such 20 that it need be taken only one time per day, then the convenience for the patients will be largely promoted.

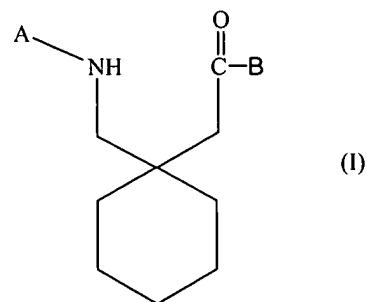
Previously, the cyclic amino acid (gabapentin) was used to conjugate with the twenty natural amino acids to produce its derivatives and increase its standing time in the body. The related art is achieved by

chemical synthesis, which describes the synthesis pathway, yet the related tests were not extended to prove the efficacy of the designed derivative.

SUMMARY OF THE INVENTION

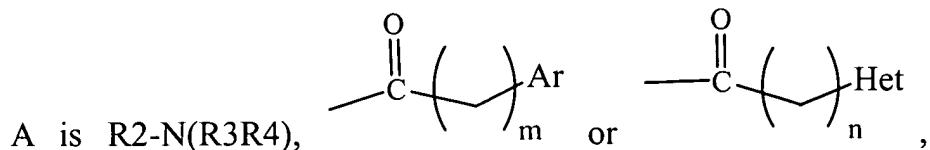
5 The object of the present invention is to provide a compound derived from gabapentin, which can be used as a prodrug of gabapentin to increase its bioavailability in vivo.

To achieve the object, the present gabapentin derivative is a compound of a formula (I):

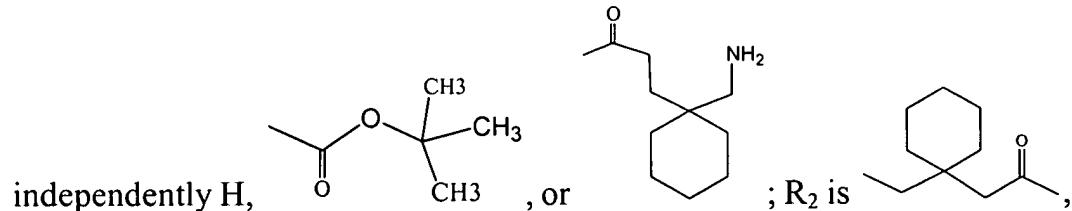


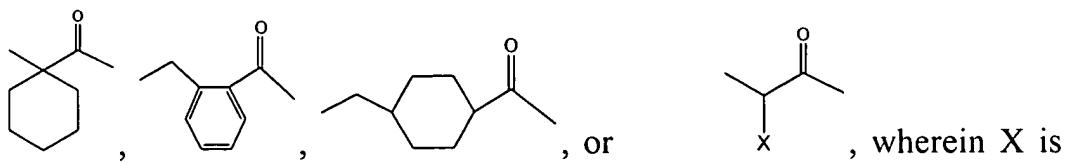
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wherein



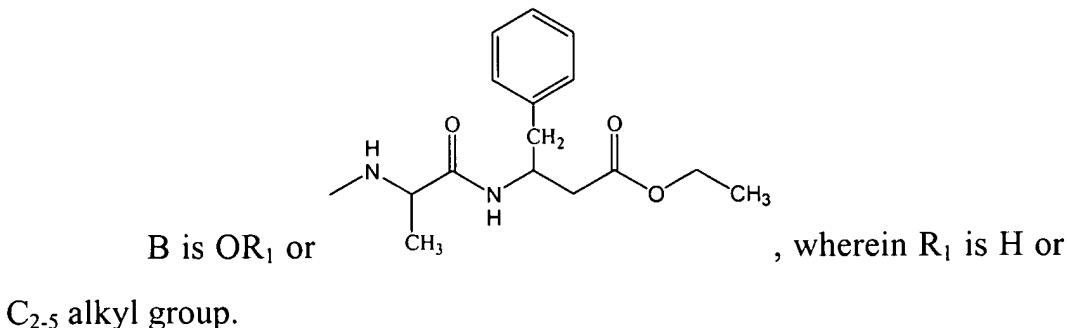
wherein Ar is a substituted or unsubstituted phenyl group, m is an integer between 0 to 4, Het is a substituted or unsubstituted 4 to 8 member heterocyclic group, n is an integer between 0 to 4; R_3 and R_4 are



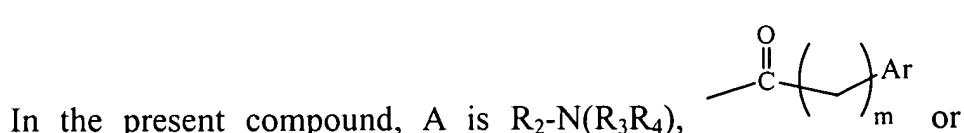


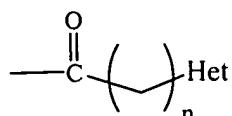
$(CH_2)_y\text{-Ar}'$, R_6 , or $(CH_2)_z\text{-Het}'$, wherein Ar' is a substituted or unsubstituted phenyl group, y is an integer between 0 to 2, R_6 is a substituted or unsubstituted linear or branched C_{1-10} alkyl group, z is an

5 integer between 0 to 2, and Het' is a 6 to 12 member heterocyclic group;

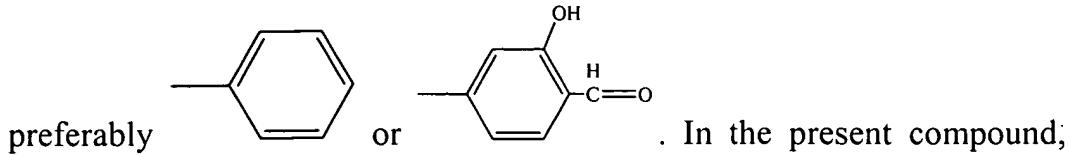


In the present invention, one or several specific unnatural amino acids are conjugated with a gabapentin moiety to produce new compounds whose hydrophobicity is better than that of the original gabapentin. The new compounds are tested in the Caco-2 cell model, and the best transmission rate of the examples is ten fold more than the parent. Therefore, the compound with gabapentin moiety of the present invention increases the oral bioavailability in human patients. Moreover, the new structure of the compounds with gabapentin moiety of the present invention is a specific achievement of the novel concept in drug design.

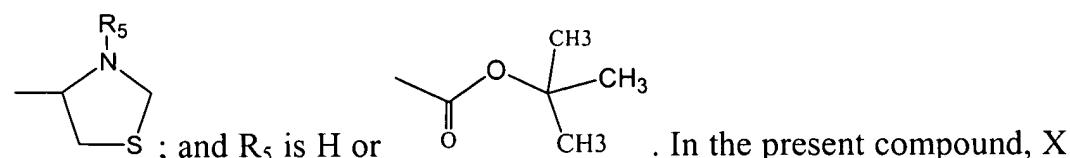
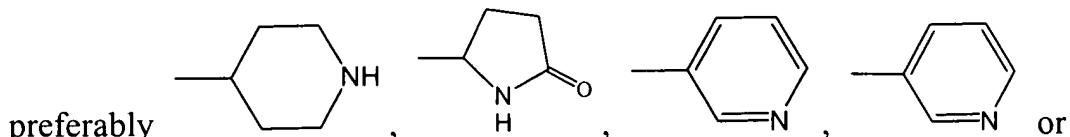




Ar^1 ⁿ , wherein Ar is a substituted or unsubstituted phenyl group,



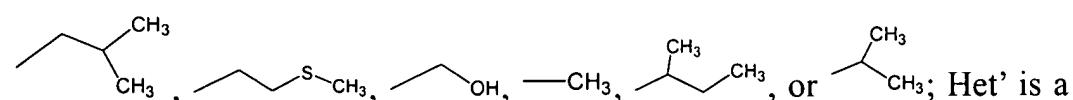
Het is a substituted or unsubstituted 4 to 8 member heterocyclic group,



preferably is $(CH_2)_y\text{-Ar}'$, R_6 , or $(CH_2)_z\text{-Het}'$, wherein Ar' is a substituted or

unsubstituted phenyl group, preferably  or ; and R_6 is a

substituted or unsubstituted linear or branched C₁₋₁₀ alkyl group, preferably



10 6 to 12 member heterocyclic group, preferably

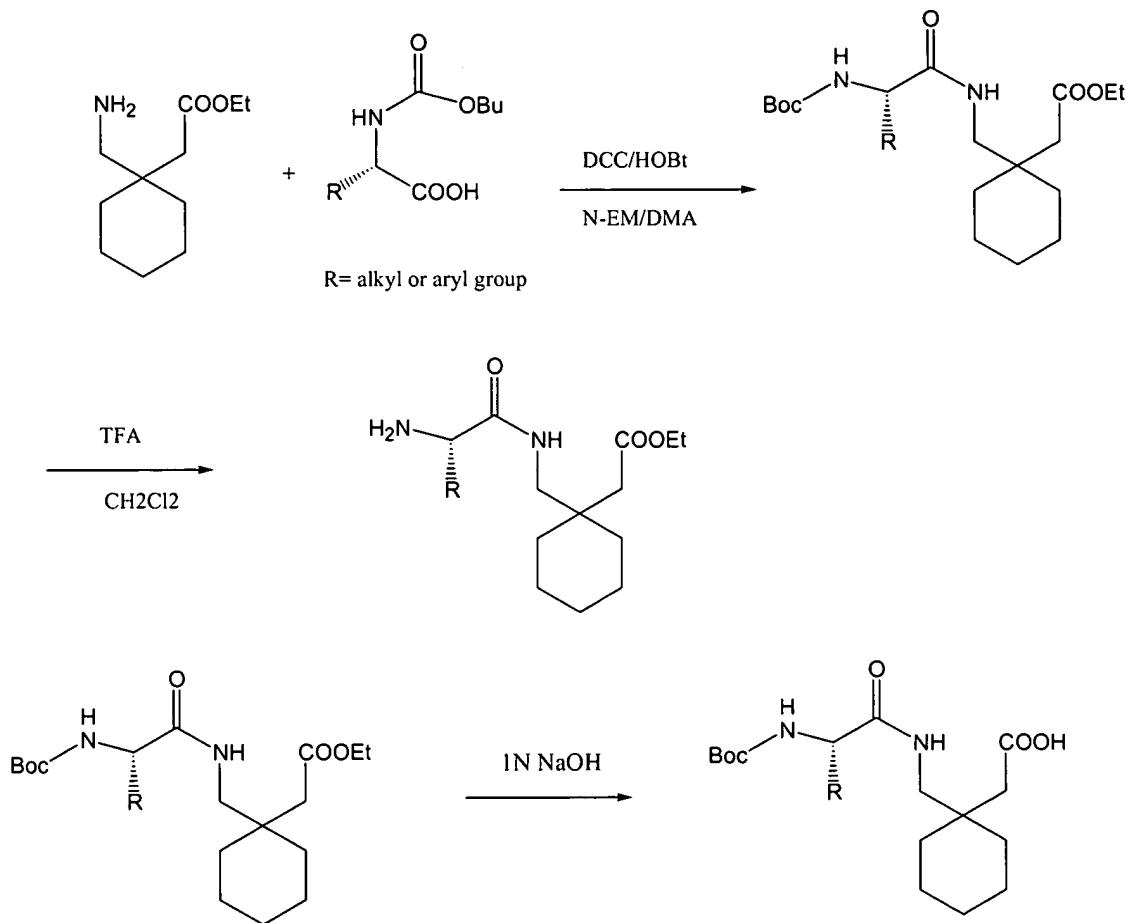
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

For the greater understanding of the present art by those skilled in the art, there are thirty-eight preferred embodiments specifically described

as follows.

In the present invention, the preparing method of each embodiment is represented by the synthesis pathways in Scheme 1.

Scheme 1



5

The establishment of the intestinal absorption model in vitro is processed by an activity selection in vitro and showed as follows:

Chemical
Modification

Caco-2
Assay

HPLC ELSD
Detection



The activity selection in vitro is used to select the gabapentin derivative.

5 The common use of the activity selection model for the in vitro intestinal absorption comprises: (1) Carcinoms (Caco-2); (2) Using Chamber; (3) Everted Gut Sac. Basically, there is no difference for those three drug-activity-selection models when they are used for evaluating the activity selection. However, in terms of the cell source from human, a cell
10 line is predominant. Moreover, with the cellular metabolism being similar to human intestines, Caco-2 becomes an excellent tool in the study of intestine absorption. Therefore, in the comparison of the in vitro transmission rate between gabapentin and gabapentin derivatives, the Caco-2 system is still the favorable model.

15 The research for studying gabapentin and the derivatives thereof in the present invention includes: Caco-2 cell activation, Caco-2 monolayer cell cultivation, resistance value measurement, effect of time to gabapentin transmission rate, and comparison of transmission rate between gabapentin and gabapentin derivatives. In constructing the Caco-2 monolayer, the
20 original cell line is the human colon adenocarcinoma cell (Caco-2), and its data sheet is listed as Table 2.

The Caco-2 cell is activated appropriately, and seeded in the transwell at 37°C in an amount of about 1×10^5 . The aliquot is cultivated in 5% CO₂ at 37°C and replaced with a fresh medium every 3 to 4 days, and

then the monolayer cell is obtained by the 21 days cultivation. The integrity of the Caco-2 cell is further characterized by tissue section and resistance value measurement.

5 Embodiment 1 Preparation of the NBoc-D-Leu.GBP.OH

In the present embodiment, the chemicals and solvents are commercially available from Aldrich®, Lancaster®, or TEDIA® chemical degree products and never purified before usage; the (1-Aminomethyl-cyclohexyl)-acetic acid ethyl ester (GBPOEt) is synthesized according to 10 the conventional methods. The IUPAC chemical nomenclature of the NBoc-D-Leu.GBP.OH is {1-[(2*R*-*tert*- Butoxycarbonylamino-4-methyl-pentanoylamino)-methyl]-cyclohexyl}- acetic acid.

0.8 g (3.4 mmol) of 2*R*-*tert*- Butoxycarbonylamino-4-methyl-pentanoic acid (BocN-D-LeuOH) is mixed with 0.8 g (3.41 mmol) of 15 (1-Aminomethyl- cyclohexyl)-acetic acid ethyl ester (GBPOEt) and then dissolved in THF (6 mL) and DMA (2 mL). Then 460 μ l (3.74 mmol) of N-ethylmorpholine (N-EM) and 0.52g (3.74 mmol) of 1-hydroxybenzotriazole hydrate (HOBT) are further added. After 20 dissolving completely, the solvent is cooled to 0°C, then 0.76 g (3.74 mmol) of 1,3-dicyclohexylcarbodiimide (DCC) is added and stirred for 1 hr. After the temperature is returned to 25 to 27°C, the mixture is stirred for another 10 to 15 hr. Then, the solid portion is filtrated, and the filtrate is diluted with 25 ml of ethyl acetate, and further washed individually and orderly with 10 ml of saturated NaHCO₃, 10% of citric acid, and saturated NaHCO₃. The

organic layer is dried, filtrated, and concentrated to remove the solvent fraction and obtain the crude product. The crude product is further chromatographically filtrated by alumina oxide with the elute solvent of ethyl acetate/hexane 2:1 to obtain 0.69 g of a viscous liquid product (yield: 5 49.3%).

¹H NMR (200MHz, CDCl₃): δ 0.94 (d, J=5.29 Hz, 6H), 1.30 (t, J=7.12 Hz, 3H), 1.21-1.72 (m, 15H, cyclohexyl, Leucine-CH₂CH₂CH-), 1.43 (9H, t-butyl), 2.29 (s, 2H), 3.25-3.31 (m, 2H), 4.06-4.20 (m, 4H), 4.96 (br d, J=7.80 Hz, 2H), 6.85 (br s, 2H).

10

Further, 0.69 g of {1-[(2-*tert*-Butoxycarbonylamino-4-methyl-pentanoylamino)-methyl]-cyclohexyl}-acetic acid ethyl ester and 10 ml of MeOH are added in the 50-ml bottle, then 2.5 ml of 2N NaOH is added and heated to 60°C for 1hr. After cooling, the mixture is neutralized 15 to around pH 7.0 by 3N HCl and then vacuum concentrated to a nearly viscous state. Then, 10 ml of H₂O is added and adjusted to pH ~1.0 by 3N HCl and extracted twice with 10 ml of ethyl acetate. The organic layer is further washed with 10 ml of saturated salt solution, dried with magnesium sulfate anhydride, filtrated and concentrated to obtain 0.52 g of product 20 (yield: 80.8%).

¹H NMR (200MHz, CDCl₃): δ 0.94 (d, J=5.26 Hz, 6H), 1.32-1.92 (m, 15H, cyclohexyl, Leucine-CH₂CH₂CH-), 1.44 (9H, t-butyl), 2.17 (s, 2H), 3.30 (s, 2H), 4.96 (br m, 1H), 7.29-7.34 (br m, 2H).

Embodiment 2 Preparation of the NH₂GBP-GBPOEt

The IUPAC chemical nomenclature of the NH₂GBP-GBPOEt is (1-{[2-(1-Aminomethyl-cyclohexyl)-acetyl amino]-methyl}-cyclohexyl) - acetic acid ethyl ester.

5 1.6 g (5.9 mmol) of [1-(*tert*-Butoxy-carbonylamino-methyl)-cyclohexyl] -acetic acid (BocN-GBPOH) is mixed with 1.39 g (5.9 mmol) of (1-Aminomethyl-cyclohexyl)-acetic acid ethyl ester (GBPOEt) and then dissolved in THF (8 mL) and DMA (4 mL). Then 820 μ l (6.49 mmol) of N-ethylmorpholine (N-EM) and 0.8 g (6.49 mmol) of 10 1-hydroxybenzotriazole hydrate (HOBT) are further added. After dissolving completely, the solvent is cooled to 0-5°C; then 1.33 g (6.49 mmol) of 1,3-dicyclohexylcarbodiimide (DCC) is added and stirred for 1 hr. After the temperature is returned to 25 to 27°C, the mixture is stirred for another 18 hr. Then, the solid portion is filtrated, and the filtrate is diluted 15 with 25 ml ethyl acetate, and further washed individually and orderly with 15 ml of saturated NaHCO₃, 10% of citric acid, and saturated NaHCO₃. The organic layer is dried, filtrated, and concentrated to remove the solvent fraction and obtain the crude product. The crude product is further chromatographically filtrated by alkali aluminum oxide with the elute 20 consisting of ethyl acetate/hexane (1:3) to obtain 2.06 g of a white viscous liquid product [1-({2-[1-(*tert*-Butoxy- carbonylamino-methyl)-cyclohexyl]-acetyl amino}- methyl)-cyclohexyl]-acetic acid ethyl ester.

¹H NMR (200MHz, CDCl₃): δ 1.26 (t, J=7.10 Hz, 3H), 1.25-1.82 (m, 20H, cyclohexyl), 1.43 (9H, t-butyl), 2.15 (s, 2H), , 2.32 (s, 2H), 3.13 (d,

J=6.80 Hz, 2H), 3.30 (d, J=6.20 Hz, 2H) 4.08-4.20 (m, 2H), 5.46-5.52 (br m, 1H), 7.02 (br s, 1H).

Further, 2.06 g of [1-({2-[1-(*tert*-Butoxycarbonylamo-n-methyl)-cyclohexyl]-acetylamo-n}-methyl)-cyclohexyl]-acetic acid ethyl ester (the 5 productivity of 77.1%) and 13 ml of CH₂Cl₂ are added in the 50-ml bottle. Then, 2.5 ml of trifluoroacetic acid is added under 25°C, and stirred at 25 to 28°C for 3hr. The mixture is further vacuum concentrated to a nearly viscous state and diluted with 20 ml ethyl acetate. Then, the mixture is extracted twice with 10 ml of saturated NaHCO₃. The organic layer is 10 further washed with 10 ml of a saturated salt solution, dried with magnesium sulfate anhydride, filtrated and concentrated to obtain 1.6 g of a final product (yield: 99%).

¹H NMR (200MHz, CDCl₃): δ 1.26 (t, J=7.10 Hz, 3H), 1.25-1.72 (m, 20H, cyclohexyl x2), 2.32 (s, 2H), 2.45 (s, 2H), 2.97 (s, 2H), 3.26 (d, 15 J=6.00 Hz, 2H), 4.14- (q, J=7.10 Hz, 2H), 6.8 (br s, 1H), 7.21-7.28 (m, 1H).

Embodiments 3 to 38

Embodiments 3 to 38 are similar methods wherein the products are prepared as Table 1.

20 The results of the cell transmission rate in the products of embodiments 3 to 38 are further listed in Table 1.

Table 1 The results of products and cell transmission rate in the
embodiments

No. of Embodiment	Sample Name and IUPAC Nomenclature	MW.	Analysis Method	Caco-2 Cell Mean Total Transmission rate 4h (%)	gbp-prodrug/ gbp Transmission Fold
Control 1	GBP.HCl	171+36.45	ELSD	1.1	1
Embodiment 1	NBoc-D-Leu.GBP.OH {1-[2-tert-Butoxycarbonylamino-4-methyl-pentanoylamino]-methyl}-cyclohexyl}-acetic acid	384	ELSD	29	26.4
Embodiment 2	NH ₂ GBP-GBPOEt(1-[2-(1-Aminomethyl-cyclohexyl)-acetylamino]-methyl}-cyclohexyl)-acetic acid ethyl ester	352	ELSD	10.25	9.3
Embodiment 3	NBoc-D-PhG.GBP.OH {1-[2-tert-Butoxycarbonylamino-2-phenyl-acetylamino)-methyl]-cyclohexyl}-acetic acid	404	ELSD	3.1	2.8
Embodiment 4	NBoc-D-Phe.GBP.OH {1-[2-tert-Butoxycarbonylamino-3-phenyl-propionylamino]-methyl}-cyclohexyl}-acetic acid	418	ELSD	10	9.1
Embodiment 5	NBoc-D-Met.GBP.OH {1-[2-tert-Butoxycarbonylamino-4-methylsulfanyl-butylamino]-methyl}-cyclohexyl}-acetic acid	402	ELSD	26	23.6
Embodiment 6	NBoc.GBP.GBP.OH [1-({2-[1-(tert-Butoxycarbonyl-amino-methyl)-cyclohexyl]-acetylamino}-methyl)-cyclohexyl]-acetic acid	424	ELSD	27	24.5
Embodiment 7	NH ₂ .INP.GBP.OEt (1-{{(Piperidine-4-carbonyl)-amino}-methyl}-cyclohexyl)-acetic acid ethyl ester	310	ELSD	1	0.9
Embodiment 8	Tol-NHGBP.OEt [1-(Benzoylamino-methyl)-cyclohexyl]-acetic acid ethyl ester	317	ELSD	21.4	19.5

Embodiment 9	NH2-ACHC.GBP.OEt <i>{1-[(1-Amino-cyclohexanecarbonyl)-amino]-methyl}-cyclohexyl}-acetic acid ethyl ester</i>	324	ELSD	10.4	9.5
Embodiment 10	NBocD-Ser-GBPOH <i>{1-[(2-tert-Butoxycarbonylamino-3-hydroxy-propionylamino)-methyl]-cyclohexyl}-acetic acid</i>	358	ELSD	20.7	18.8
Embodiment 11	NH2.D-Ala-GBPOEt <i>{1-[(2-Amino-propionylamino)-methyl]-cyclohexyl}-acetic acid ethyl ester</i>	270	ELSD	17.6	16.0
Embodiment 12	NH2.GBP-D-Ala-L-PheOEt <i>2-{2-[2-(1-Aminomethyl-cyclohexyl)-acetylamino]-propionylamino}-3-phenyl-propionic acid ethyl ester</i>	417	ELSD	2.83	2.6
Embodiment 13	NH2D-Leu-GBPOEt <i>{1-[(2-Amino-4-methyl-pentanoylamino)-methyl]-cyclohexyl}-acetic acid ethyl ester</i>	312	ELSD	12.37	11.2
Embodiment 14	NH2D-Ser-GBPOEt <i>{1-[(2-Amino-3-hydroxy-propionylamino)-methyl]-cyclohexyl}-acetic acid ethyl ester</i>	292	ELSD	10.95	10.0
Embodiment 15	NBocD-Phe-GBPOH <i>{1-[(2-tert-Butoxycarbonylamino-3-phenyl-propionylamino)-methyl]-cyclohexyl}-acetic acid</i>	418	ELSD	0.93	0.8
Embodiment 16	NH2D-Phe-GBPOEt <i>{1-[(2-Amino-3-phenyl-propionylamino)-methyl]-cyclohexyl}-acetic acid ethyl ester</i>	346	ELSD	10.30	9.4
Embodiment 17	NH2L-Ile-GBPOEt <i>{1-[(2-Amino-3-methyl-pentanoylamino)-methyl]-cyclohexyl}-acetic acid ethyl ester</i>	312	ELSD	9.47	8.6

Embodiment 18	$\text{NH}_2\text{-2-MePhe-GBPOEt}$ $\{1-[2\text{-Aminomethyl-benzoyl amino}\text{-methyl}\text{-cyclohexyl}\text{-acetic acid ethyl ester}$	360	ELSD	2.13	1.9
Embodiment 19	$\text{NH}_2\text{-CH2-4-Cyhexyl-GBPOEt}$ $\{1-[2\text{-[4\text{-Aminomethyl-cyclohexanecarbonyl}\text{-amino}\text{-methyl}\text{-cyclohexyl}\text{-acetic acid ethyl ester}$	338	ELSD	11.14	10.1
Embodiment 20	$\text{NH}_2\text{GBP.D-Leu-GBPOEt}$ $\{1-[2\text{-[2\text{-[1\text{-Aminomethyl-cyclohexyl}\text{-acetyl}\text{amino}\text{-4\text{-methyl-pentanoyl}\text{amino}\text{-methyl}\text{-cyclohexyl}\text{-acetic acid ethyl ester}$	465	ELSD	12.22	11.1
Embodiment 21	$\text{NH}_2\text{GBP.D-Phg-GBPOEt}$ $\{1-[2\text{-[2\text{-[1\text{-Aminomethyl-cyclohexyl}\text{-acetyl}\text{amino}\text{-2\text{-phenyl}\text{-acetyl}\text{amino}\text{-methyl}\text{-cyclohexyl}\text{-acetic acid ethyl ester}$	485	ELSD	8.58	7.8
Embodiment 22	$\text{NH}_2\text{GBP.D-Phe-GBPOEt}$ $\{1-[2\text{-[2\text{-[1\text{-Aminomethyl-cyclohexyl}\text{-acetyl}\text{amino}\text{-3\text{-phenyl}\text{-propionyl}\text{amino}\text{-methyl}\text{-cyclohexyl}\text{-acetic acid ethyl ester}$	499	ELSD	9.26	8.4
Embodiment 23	$\text{NH}_2\text{GBP.L-Pro-GBPOEt}$ $\{1-[2\text{-[1\text{-[2\text{-[1\text{-Aminomethyl-cyclohexyl}\text{-acetyl}\text{-pyrrolidin-2\text{-carbonyl}\text{-amino}\text{-methyl}\text{-cyclohexyl}\text{-acetic acid$	449	ELSD	10.73	9.8
Embodiment 24	$(3\text{-OMe4OH})\text{Ph-GBPOEt}\{1-[4\text{-Hydroxy-3\text{-methoxy-benzoyl}\text{amino}\text{-methyl}\text{-cyclohexyl}\text{-acetic acid ethyl ester}$	349	ELSD	13.59	12.4
Embodiment 25	Pydone-GBPOEt($1\text{-[5\text{-Oxo-pyrrolidine-2\text{-carbonyl}\text{-amino}\text{-methyl}\text{-cyclohexyl}\text{-acetic acid ethyl ester}$	310	ELSD	5.68	5.2

Embodiment 26	$\text{NH}_2\text{D}-\text{Met-GBPOEt}\{1-[(2\text{-Amino-4-methylsulfanylbutyryl})-\text{methyl}]-\text{cyclohexyl}\}-\text{acetic acid ethyl ester}$	330	ELSD	9.02	8.2
Embodiment 27	$\text{3pyridine-GBPOEt}\{1-[(\text{Pyridine-3-carbonyl})-\text{amino}]-\text{methyl}\}-\text{cyclohexyl}\}-\text{acetic acid ethyl ester}$	304	ELSD	9.39	8.5
Embodiment 28	$\text{NH}_2\text{D-Ala-GBPOEt}\{1-[(2\text{-Amino-propionylamino})-\text{methyl}]-\text{cyclohexyl}\}-\text{acetic acid ethyl ester}$	270	ELSD	8.11	7.4
Embodiment 29	$\text{NH}_2\text{D-Val-GBPOEt}\{1-[(2\text{-Amino-3-methylbutyryl})-\text{amino}-\text{methyl}]-\text{cyclohexyl}\}-\text{acetic acid ethyl ester}$	298	ELSD	8.73	7.9
Embodiment 30	$\text{NH}_2\text{L-Phg-GBPOEt}\{1-[(2\text{-Amino-2-phenyl-acetyl})-\text{amino}-\text{methyl}]-\text{cyclohexyl}\}-\text{acetic acid ethyl ester}$	332	ELSD	11.87	10.8
Embodiment 31	$\text{NH}_2\text{D-hPhe-GBPOEt}\{1-[(2\text{-Amino-4-phenylbutyryl})-\text{amino}-\text{methyl}]-\text{cyclohexyl}\}-\text{acetic acid ethyl ester}$	358	ELSD	12.30	11.2
Embodiment 32	$\text{NH}_2\text{L-hPhe-GBPOEt}\{1-[(2\text{-Amino-4-phenylbutyryl})-\text{amino}-\text{methyl}]-\text{cyclohexyl}\}-\text{acetic acid ethyl ester}$	358	ELSD	1.76	1.6
Embodiment 33	$\text{NH}_2\text{D-Try-GBPOEt}\{1-[(2\text{-Amino-2-(1H-indol-2-yl)-acetyl})-\text{amino}-\text{methyl}]-\text{cyclohexyl}\}-\text{acetic acid ethyl ester}$	385	ELSD	9.97	9.1
Embodiment 34	$\text{NH}_2\text{L-Thz-GBPOEt}\{1-[(\text{Thiazolidine-4-carbonyl})-\text{amino}-\text{methyl}]-\text{cyclohexyl}\}-\text{acetic acid ethyl ester}$	314	ELSD	4.50	4.1

Embodiment 35	<chem>NH2L-Tyr-GBPOEt</chem> <i>(1-{{2-Amino-2-(4-hydroxy-p-phenyl)-acetylamino]-methyl}-cyclohexyl)-acetic acid ethyl ester</i>	362	ELSD	10.33	9.4
Embodiment 36	<chem>(3-Py)CH2CH2GBPOEt</chem> <i>[1-{{3-[(Pyridine-3-carbonyl)-amino]-propionylamino}-methyl}-cyclohexyl]-acetic acid ethyl ester</i>	375	ELSD	9.00	8.2
Embodiment 37	<chem>NBocL-Thz-GBPOEt</chem> <i>4-[(1-Ethoxycarbonylmethyl-cyclohexylmethyl)-carbamoyl]-thiazolidine-3-carboxylic acid tert-butyl ester</i>	414	ELSD	6.13	5.6
Embodiment 38	<chem>NBocL-Tyr-GBPOEt</chem> <i>(1-{{2-tert-Butoxycarbonyl-amino-2-(4-hydroxy-phenyl)-acetylamino]-methyl}-cyclohexyl)-acetic acid ethyl ester</i>	462	ELSD	5.05	4.6

HPLC Analysis: Intersil ODS-3V 250*4.6 mm column, Solvent: MeOH / H₂O = 10 : 90 to 70 : 30 with 0.1% of NH₄OAc, Flow rate = 1.0 ml/min, ELSD: Evaporative Light Scattering Detector. Every derivative has been repeated for 3 times in analysis, 4 hr later, the sample is analyzed for the transmission rate and then averaged to account its transmission fold.

Table 2 Human Colon Adenocarcinoma Cell Line Strain Data Sheet

Strain Code No.	CCRC60018		
Cell Line	Caco-2		
Cell Strain Source	ATCC HTB-37		
Tissue Source	Colon, adenocarcinoma, human		
Frozen Tube Volume	1 ml	Concentration	1.3×10^6
Frozen Date	12. 31.1999	Subculture No.	P23
Survival Rate	82.5%		

Medium	80% MEM (Eagle) with non-essential amino acids and Earle's BSS +20%FBS
Cultivation Condition	37°C, 5% CO ₂
Frozen Medium	90% culture medium+10% DMSO
Medium Replacement	2 to 3 times per week
Subculture Dilution Ratio	1:2 to 1:3
Contamination Test	Negative for bacteria, fungi and mycoplasma

Furthermore, for increasing the efficiency of drug-absorption through oral administration, these drugs are designed to pass the epithelium cells in small intestines by passive diffusion can enter the “body circulation”. For facilitating the passive diffusion of drugs through the epithelium cells in small intestines, several biochemical features of the drugs are adjusted. These biochemical features of the suitable drugs comprise low molecular weight (such as <500Da), water solubility, and proper hydrophilicity/hydrophobicity ratio (1.5 < log P <4.0, with reference: 5 Navia, chaturvedi, P.R. *Drug Discovery Today*, 1996, 1, 179-189). On the other hand, because gabapentin is a compound with high polarity and high 10 hydrophilicity (log P = -1.1), gabapentin or its derivative is hard to pass the lipid layer of the small intestines epithelium cells. Therefore, compounds modified from the structure of gabapentin or its derivatives (as listed in 15 Table 1) for functioning as prodrugs facilitate the passive diffusion through the epithelium cells in small intestines for entering blood circulation.

Embodiment 39 Oral drug absorption test

Rats (3 male, Winstar rats) are fed with 300mg/kg dosage of 20 compounds. Plural blood samples are collected at different times (0, 0.5, 1,

2, 3, 8, 12, 24 hrs). The blood samples are centrifuged, and the concentration of gabapentin in the serum are analyzed with LC/MS/MS (MRM method, limitation of instruments 0.005 μ g/mL). The results are listed in Table 3.

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Table 3: Gabapentin prodrug concentration in rat blood (passive diffusion passage)

Compound	Tmax ** (hr)	C max *** (mg/mL)	AUC**** (mg.hr/mL)
Embodiment 2 NH ₂ .GBP.GBPOEt	1.0	34.4	198.56
Embodiment 29 NH ₂ .D-ValGBPOEt	3.5	0.46	2.66
Gabapentin HCl*	2.0	2.53	13.30

*: Gabapentin HCl is synthesized by the inventor;

**Tmax: the timing of maximum concentration of Gabapentin ;

10 ***Cmax: the maximum concentration of Gabapentin in blood;

****AUC: the area sum under the Gabapentin concentration curve, the higher value means the better absorption by intestine, calculated by WinNonLin®.

The AUC value of the compound from Embodiment 2 is 14.9 times
15 higher than Gabapentin HCl. The fact means that compound prepared in
embodiment 2 enters blood circulation easily.

After reducing the dosage, compounds of gabapentin prodrugs were selected for further pharmacodynamic analysis. The rats are fed with 50 mg/kg dosage of gabapentin equivalency individually. The results are listed
20 in Table 4. The results showed gabapentin prodrugs could be absorbed in

animal intestine and degraded by intestinal enzymes to release gabapentin.

Table 4: Gabapentin released by prodrug blood analysis results in Rat

Compound	Tmax (hr)	Cmax (mg/mL)	AUC(μ g.hr/mL)
Embodiment 2 NH ₂ .GBP.GBPOEt	2.0	1.00	4.27
NH ₂ .Gly GBPOH	1.0	22.0	81.40
NH ₂ .L-Phe.GBPOH	2.0	2.71	44.37
Gabapentin HCl	1.0	32.3	122.26

5 NH₂.Gly.GBPOH prodrug can release gabapentin in the animal blood with an AUC value of 81.4, which is 0.67 times higher than that of gabapentin. On the other hand, although the maximum concentration Cmax of prodrug is lower than that of gabapentin, which also means lower side effect while still having effective concentration.

10 The experiments illustrated above in Embodiment 39 prove that the gabapentin derivatives in a prodrug form can ease the absorption of gabapentin derivatives by intestinal diffusion, and the gabapentin prodrugs in the blood promise the releasing of gabapentin. The prodrug idea can be further applied to other drugs.

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From the above embodiments, it is found that the present gabapentin derivatives certainly enhance the cell transmission rate and promote the bioavailability of the prodrug for the better potency.

20 Although the present invention has been explained in relation to its preferred embodiment, it is to be understood that many other possible

modifications and variations can be made without departing from the spirit and scope of the invention as hereinafter claimed.